

0701.113B

S-LANSOPRAZOLE COMPOSITIONS AND METHODS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the priority of US
provisional applications 60/073,141, filed January
5 30, 1998, and 60/107,460, filed November 5, 1998, the
disclosures of which are incorporated herein by
reference.

FIELD OF THE INVENTION

This invention relates to compositions of matter
10 containing lansoprazole. The invention also relates
to methods of treating and preventing ulcers,
treating other conditions related to gastric
hypersecretion, and treating psoriasis.

BACKGROUND OF THE INVENTION

15 Racemic lansoprazole is an orally active,
potent, irreversible inhibitor of H^+, K^+ -ATPase. The
compound is one of the class of compounds known as
gastric "proton pump" inhibitors. These compounds
are weak organic bases which diffuse passively from
20 the plasma into the acid-containing intracellular
canaliculi of gastric parietal cells. At the low pH
found in the lumen of these canaliculi, the
protonated compounds rearrange to form pyridinium
sulfenamides, which react with sulfhydryl groups
25 present on the ATPase localized in the membranes
lining the intracellular canaliculi. The alkylation
of the sulfhydryl inhibits the ability of the enzyme

0701.113B

to catalyze the secretion of H^+ into the lumen in exchange for K^+ ions. This inhibition results in an overall reduction in hydrochloric acid secretion by the parietal cells into the cavity of the stomach, thus increasing intragastric pH. As a consequence of reduced acidity in the stomach, the activity of the proteolytic enzyme pepsin is also markedly decreased. Because the proton pump is the final step in acid production and the compounds of this class combine covalently with the associated H^+, K^+ -ATPase, a profound and prolonged inhibition of gastric acid secretion can be achieved.

Proton pump inhibitors have also been reported as useful in treating psoriasis. [See PCT application WO95/18612]

The C_{max} of racemic lansoprazole is at about 1.7 hours in humans and the serum half-life is about 1.5 hours, but this does not reflect the duration of the acid inhibitory effect, which is about 24 hours. Racemic lansoprazole is comparable to omeprazole in its effects on hepatic drug metabolizing enzyme systems.

Although no cardiovascular or obvious physical sequelae of elevated gastrin have been observed in humans on administration of racemic lansoprazole, fasting serum gastrin levels are significantly elevated. This is cause for concern because prolonged elevated serum gastrin appears to be associated with diffuse and focal enterochromaffin-like cell hyperplasia and focal neoplasia

0701.113B

(carcinoids) in rats. [Larsson et al. Gastroenterology 90, 391-399 (1986)]. Thus, despite its advantages, adverse effects of racemic lansoprazole may remain, including, but not limited to, some incidence of hepatocellular neoplasia and gastric carcinoids on long-term therapy, and headache, diarrhea and skin alterations on acute therapy. There has also been some concern about the inhibition of cytochrome P450 enzymes by racemic lansoprazole [Kromer Digestion 56, 443-454 (1995)]; this effect would lead to adverse drug-drug interactions.

The following adverse events have been reported in lansoprazole-treated patients: Body as a Whole - asthenia, candidiasis, chest pain (not otherwise specified), edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise; Cardiovascular System - angina, cerebrovascular accident, hypertension/hypotension, myocardial infarction, palpitations, shock (circulatory failure), vasodilation; Digestive System - melena, anorexia, bezoar, cardiospasm, cholelithiasis, constipation, dry mouth/thirst, dyspepsia, dysphagia, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastroenteritis, gastrointestinal hemorrhage, hematemesis, increased appetite, increased salivation, rectal hemorrhage, stomatitis, tenesmus, ulcerative colitis, vomiting; Endocrine System - diabetes mellitus, goiter, hyperglycemia/hypoglycemia, Hematologic and Lymphatic System - anemia, hemolysis; Metabolic and Nutritional

0701.113B

Disorders - gout, weight gain/loss; Musculoskeletal System - arthritis/arthralgia, musculoskeletal pain, myalgia; Nervous System - agitation, amnesia, anxiety, apathy, confusion, depression,
5 dizziness/syncope, hallucinations, hemiplegia, aggravated hostility, decreased libido, nervousness, paresthesia, thinking abnormality; Respiratory System - asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, pneumonia, upper
10 respiratory inflammation/infection; Skin and Appendages - acne, alopecia, pruritis, rash, urticaria, Special Senses - amblyopia, deafness, eye pain, visual field defect, otitis media, taste perversion, tinnitus; Urogenital System - abnormal
15 menses, albuminuria, breast enlargement/gynecomastia, breast tenderness, glycosuria, hematuria, impotence, kidney calculus.

It would therefore be particularly desirable to find a compound with the advantages of the racemic mixture
20 of lansoprazole which would not have the aforementioned disadvantages.

SUMMARY OF THE INVENTION

This invention relates to the use of optically pure S(-)lansoprazole for treating ulcers of the stomach, duodenum and esophagus, gastroesophageal reflux diseases, Zollinger-Ellison Syndrome, and other disorders including those that would benefit from an inhibitory action on gastric acid secretion. S(-)Lansoprazole inhibits the H^+ , K^+ -ATPase associated with the gastric proton pump and the resulting secretion of gastric acid by parietal cells providing therapy in diseases associated with gastric hyperacidity. The invention also relates to a method of treating psoriasis using optically pure S(-) lansoprazole. Optically pure (-) lansoprazole provides this treatment while substantially reducing adverse effects, including, but not limited to, hepatocellular neoplasia, gastrin hypersecretion, gastric neoplasms or carcinoids, headache, diarrhea and skin alterations which are associated with the administration of the racemic mixture of lansoprazole.

The invention also relates to certain oral pharmaceutical compositions containing the S(-) isomer of lansoprazole.

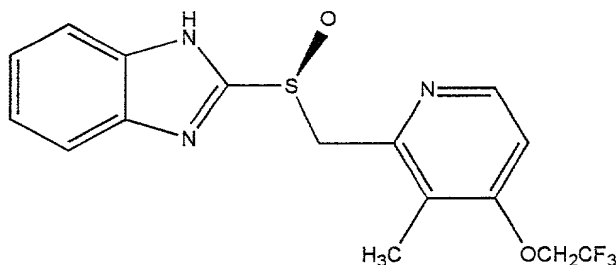
DETAILED DESCRIPTION OF THE INVENTION

The active compound of these compositions and methods is an optical isomer of lansoprazole. The preparation of racemic lansoprazole is described in United States Patents 4,628,098 and 4,689,333. The

0701.113B

medicinal chemistry and clinical aspects of racemic lansoprazole have been reviewed by Garnett [Ann. Pharmacother. 30, 1425-1436 (1996)], by Langtry and Wilde [Drugs 54, 473-500 (1997)] and by Barradell et al. [Drugs 44, 225-250 (1992)]. Chemically, the
5 active compound is the (-) isomer of 2-[3-methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl]methylsulfinyl-benzimidazole(I), hereinafter referred to as lansoprazole.

10



I

(-) Lansoprazole, which is the subject of the present invention, is not presently commercially available; only the 1:1 racemic mixture is
15 commercially available as Prevacid®.

Syntheses of R (+) lansoprazole and S(-) lansoprazole by asymmetric oxidation and by bioreduction are described in PCT applications WO 9602535 and 9617077, respectively, the disclosures of
20 which are incorporated herein by reference. The enrichment of single enantiomers by crystallization of the racemate from non-racemic mixtures is described in PCT application WO 97/02261, the disclosure of which is also incorporated herein by
25 reference.

0701.113B

The pharmacology of the individual enantiomers in canine parietal cells and gastric microsomes has been reported by Nagaya et al. [Biochem. Pharmacol. 42, 1875-1878 (1991)], who concluded that "the
5 effects of the (+) and (-) enantiomer of lansoprazole on acid formation stimulated by db-cAMP in isolated parietal cells were almost identical." Similarly, inhibition of ATPase activity in gastric microsomes by the two enantiomers did not differ significantly
10 over the range of concentrations tested.

It has now been discovered that the optically pure (-) isomer of lansoprazole is a superior agent for treating ulcers of the stomach, duodenum and esophagus, gastroesophageal reflux diseases,
15 Zollinger-Ellison Syndrome, psoriasis and other disorders, including those that would benefit from an inhibitory action on H^+, K^+ -ATPase in that it provides this effective treatment while substantially reducing the adverse effects of racemic lansoprazole
20 including, but not limited to, hepatocellular neoplasia, gastric carcinoids, headache, diarrhea and skin alterations. The S(-) isomer of lansoprazole is also a superior agent for treating ulcers and other disorders by virtue of its lessened liability for
25 drug-drug interactions and its greater predictability of dosage among patients, as discussed below. Surprisingly, it also shows a longer duration, a higher AUC (area under the curve - a composite measure of efficacy and duration), and a more rapid
30 onset as a result of lower first pass metabolism.

The present invention encompasses a method of

0701.113B

treating ulcers, which comprises administering to a human in need of such therapy, an amount of (-) lansoprazole, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate the symptoms of ulcers. The method substantially reduces the concomitant liability of adverse effects associated with the administration of the racemic compound by providing an amount which is insufficient to cause the adverse effects associated with the racemic mixture of lansoprazole.

The present invention also encompasses an oral antiulcer composition for the treatment of a human in need of antiulcer therapy, which comprises a pharmaceutically acceptable carrier for oral administration and a therapeutically effective amount of (-) lansoprazole, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer. Preferably the composition is in the form of a tablet or capsule and the amount of (-) lansoprazole in the tablet or capsule is 15, 30 or 60 mg.

The present invention further encompasses a method of treating gastroesophageal reflux disease and of treating conditions caused by or contributed to by gastric hypersecretion. Conditions associated with hypersecretion in humans may include, but are not limited to, Zollinger-Ellison syndrome.

The present invention further encompasses a method of treating psoriasis while substantially

0701.113B

reducing the adverse effects of racemic lansoprazole.

Utilizing the optically pure or substantially optically pure isomer of (-) lansoprazole results in enhanced efficacy, diminished adverse effects, and accordingly, an improved therapeutic index. It also provides more rapid onset and longer duration of the therapeutic effect. Moreover, the S(-) enantiomer exhibits fewer drug-drug interactions and shows less variation in the patient population between so-called good metabolizers and poor metabolizers. It is therefore, more desirable to use the (-) isomer of lansoprazole than to administer the racemic mixture because predictability of an effective and safe dose for an individual patient is greater. The S(-) enantiomer of lansoprazole is metabolized by both CYP2D6 and CYP3A4; the R(+) enantiomer is metabolized only by CYP2D6, which is the polymorphically expressed enzyme. Because it is metabolized by both enzymes, the S(-) shows less variability in the patient population and a more predictable dosage regimen. Surprisingly, the S(-) isomer also shows a longer duration, a higher AUC and a more rapid onset as a result of lower first pass metabolism.

The term "adverse effects" includes, but is not limited to, hepatocellular neoplasia, gastrin hypersecretion, gastric carcinoids, headache, diarrhea, skin alterations and drug-drug interactions.

The term "substantially free of its (+) stereoisomer" as used herein means that the

0701.113B

compositions contain at least 90% by weight of (-)
lansoprazole and 10% by weight or less of (+)
lansoprazole. In a more preferred embodiment the
term "substantially free of the (+) isomer" means
5 that the composition contains at least 99% by weight
of (-) lansoprazole, and 1% or less of (+)
lansoprazole. These percentages are based upon the
total amount of lansoprazole in the composition. The
terms "substantially optically pure (-) isomer of
10 lansoprazole" or "substantially optically pure (-)
lansoprazole" and "optically pure (-) isomer of
lansoprazole" and "optically pure (-) lansoprazole"
are also encompassed by the above-described amounts.

The term "treating ulcers" as used herein means
15 treating, alleviating or palliating such conditions,
and thus providing relief from the symptoms of
nausea, heartburn, post-prandial pain, vomiting, and
diarrhea.

The term "a method for treating gastroesophageal
20 reflux diseases in a human" as used herein means
treating, alleviating or palliating the conditions
that result from the backward flow of the stomach
contents into the esophagus.

The term "treating a condition caused, or
25 contributed to, by gastric hypersecretion in a human"
as used herein means treating, alleviating or
palliating such disorders associated with
hypersecretion, thus providing relief from the
symptoms of the aforementioned conditions.
30 Zollinger-Ellison Syndrome is among the conditions

0701.113B

caused by or contributed to by hypersecretion.

The term "treating psoriasis" as used herein means treating, alleviating or palliating the condition, and thus providing relief from the symptoms of pruritis, epidermal scaling, itching and burning.

The magnitude of a prophylactic or therapeutic dose of (-) lansoprazole in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose and perhaps the dose frequency will also vary according to the age, body weight and response of the individual patient. In general, the total daily dose range for (-) lansoprazole for the conditions described herein is from about 10 mg to about 180 mg in single or divided doses. Preferably a daily dose range should be about 15 mg to about 60 mg in single or divided doses. In managing the patient, the therapy should be initiated at a lower dose, perhaps at about 10 mg to about 15 mg and increased up to about 60 mg or higher depending on the patient's global response. It is further recommended that children and patients over 65 years and those with impaired renal or hepatic function, initially receive low doses, and that they be titrated based on individual response(s) and blood level(s). It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in

0701.113B

conjunction with individual patient response. The terms "an amount sufficient to alleviate or palliate ulcers but insufficient to cause said adverse effects," "an amount sufficient to alleviate the symptoms of gastroesophageal reflux but insufficient to cause said adverse effects," "an amount sufficient to alleviate gastric hypersecretion but insufficient to cause said adverse effects" and "an amount sufficient to treat psoriasis" are encompassed by the above-described dosage amounts and dose frequency schedule.

The relative activity, potency and specificity of optically pure lansoprazole and racemic lansoprazole both as gastric antisecretory agents and plasma gastrin elevating agents can be determined by a pharmacological study in animals according to the method of Decktor et al. [J. Pharmacol. Exp. Ther. 249, 1-5 (1989)]. The test provides an estimate of relative activity, potency and, through a measure of specificity, an estimate of therapeutic index. Fasted rats, implanted with a gastric cannula, receive single oral or parenteral doses of (+) lansoprazole, (-) lansoprazole or racemate, 1 hour before collection of gastric juice over a four hour period. Acid output and pH are then determined on each sample. Dose response evaluations are performed with each compound to determine the lowest dose which inhibits acid output by at least 95% and maintains gastric pH above 7.0. Plasma gastrin levels are then determined in a second group of rats treated with the doses selected in the first series of tests. Blood samples are taken for analyses over the five hour

0701.113B

period after dosing, and both peak level as well as area-under-the-curve analyses of the gastrin responses are made. These responses are then analyzed statistically using Student's "t" test to
5 assess whether equivalent antisecretory doses show differences in gastrin responses.

Any suitable route of administration may be employed for providing the patient with an effective dosage of (-) lansoprazole. Rectal, parenteral
10 (subcutaneous, intramuscular, intravenous), transdermal, topical and like forms of administration are possible; oral administration is preferred. Oral dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, and the like.

15 The pharmaceutical compositions of the present invention comprise (-) lansoprazole as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic
20 ingredients.

The terms "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic bases. Since the compound of the present
25 invention is a weak acid and is unstable at low pH, salts may be prepared from pharmaceutically acceptable non-toxic bases including inorganic and organic bases. Suitable pharmaceutically acceptable base addition salts for the compound of the present
30 invention include metallic salts of aluminum,

0701.113B

calcium, lithium, magnesium, potassium, sodium,
titanium and zinc or organic salts made from lysine,
N,N'-dibenzylethylenediamine, chlorprocaine,
choline, diethanolamine, ethylenediamine, meglumine
5 (N-methylglucamine) and procaine. If any salt is to
be used, sodium salts are preferred.

The compositions of the present invention
include suspensions, solutions, elixirs or solid
dosage forms. Carriers such as starches, sugars, and
10 microcrystalline cellulose, diluents, granulating
agents, lubricants, binders, disintegrating agents,
and the like are suitable in the case of oral solid
preparations (such as powders, capsules, and
tablets), and oral solid preparations are preferred
15 over the oral liquid preparations. It has been
found that the inclusion of basic salts of calcium
and magnesium in the compositions allows the
preparation of tablets and capsules having
lansoprazole in a non-salt form and yet retaining
20 good stability. If desired, tablets and granules may
be coated by standard aqueous or nonaqueous
techniques. Oral dosage forms suitable for
lansoprazole are described in US patent 5,035,899 and
in PCT applications WO96/01624, WO97/12580 and
25 WO97/25030, the disclosures of which are incorporated
herein by reference.

In addition to the common dosage forms set out
above, the compounds of the present invention may
also be administered by controlled release
30 formulations, which are well known in the art.
Compositions suitable for rectal administration are

0701.113B

described in European Application 645140, the disclosure of which is incorporated herein by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid

0701.113B

diluent. Desirably, each tablet contains from about 5 mg to about 180 mg of the active ingredient, and each cachet or capsule contains from about 5 mg to about 180 mg of the active ingredient. Most preferably, the tablet, cachet or capsule contains one of three dosages: about 15 mg, about 30 mg or about 60 mg of (-) lansoprazole for oral administration.

The invention is further defined by reference to the following examples describing in detail the preparation of the compositions of the present invention, as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention.

EXAMPLES

Example 1 - Tablets

Composition per tablet:		
20	S(-) lansoprazole	30 mg
	Precipitated calcium carbonate	50 mg
	Corn Starch	40 mg
	Lactose	73.4 mg
	Hydroxypropylcellulose	6 mg
25	Magnesium stearate	(0.05 ml)
	Total	200.0 mg

0701.113B

EXAMPLE 1

S(-) Lansoprazole, precipitated calcium carbonate, corn starch, lactose and hydroxypropylcellulose are mixed together, water is added, and the mixture is kneaded, then dried in vacuum at 40° C. for 16 hours, ground in a mortar and passed through a 16-mesh sieve to give granules. To this is added magnesium stearate and the resultant mixture is made up into tablets each weighing 200 mg on a rotary tableting machine.

Example 2 - Granules

Composition per tablet:	
S(-) lansoprazole	30 mg
Magnesium carbonate	20 mg
Corn Starch	80 mg
Microcrystalline cellulose	20 mg
Carboxymethylcellulose calcium	10 mg
Hydroxypropylcellulose	10 mg
Pluronic F68	4 mg
Lactose	26 mg
Water	(0.05 ml)
Total	200 mg

EXAMPLE 2

The ingredients above are mixed well in the proportions shown, water is added, and the mixture is kneaded and granulated in an extruder granulator (screen size 1.0 mm ϕ). The granules are immediately

1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398	2399	2400	2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412	2413	2414	2415	2416	2417	2418	2419	2420	2421	2422	2423	2424	2425	2426	2427	2428	2429	2430	2431	2432	2433	2434	2435	2436	2437	2438	2439	2440	2441	2442	2443
------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------

5 Example 3 - Capsules

10

15

20

25

30

Enteric granules are produced by coating the granules obtained in Example 2 with the enteric coating composition shown using a fluidized bed granulator under conditions such that the inlet air temperature is 50° C. and the granule temperature is about 40° C. Number 1 hard capsules are filled with the enteric granules thus obtained in an amount of 260 mg per capsule using a capsule filling machine.

- 18 -

0701.113B

Tablets of other strengths may be prepared by altering the ratio of active ingredient to the excipients or to the final weight of the tablet. An enteric coating, such as the polyacrylate Eudragit L® and Eudragit S® series, is applied by spray coating the tablets, preferably with an aqueous dispersion of the coating polymer.